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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,676	12/01/1998	MICHAEL R. ZALUTSKY	00250.74943	4498

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/203,676	ZALUTSKY, MICHAEL R.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,14-21 and 44-48* is/are rejected.

7)☒ Claim(s) *2, 11, 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 1, 5-8 and 10 have been amended. Claim 48 has been added. Claims 1-21 and 44-48 are pending and under consideration.

The rejection of claims 1-9, 11-21 and 44-47 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed is withdrawn in light of applicants arguments.

The rejection of claims 1, 3-5, 8-10, 14-20 and 44 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199, cited in a previous Office action) and Zalutsky et al (U.S. 5,302,700, cited in a previous Office action) in view of Barnett et al (CA 209465), Woo et al (U.S. 5,130,116), the abstract of Reist et al (Cancer research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140 is maintained for reasons of record.

Claim 1 is drawn in part to a composition for internally labeling a cell comprising a ligand which specifically binds to a cell surface antigen and is internalized by the cell, wherein the ligand is an antibody, an oligopeptide which comprises at least one positively charged amino acid molecule and at least one D-amino acid residue, wherein the oligopeptide does not comprise two or more contiguous L-amino acids, wherein said oligopeptide is covalently bound to the ligand and wherein said oligopeptide does not specifically bind to the surface antigen, and a label which is covalently bound to the oligopeptide. Claim 3 embodies the composition of claim 1 wherein the label is defined by the chemical structure of II. Claim 4 embodies the composition of claim 3 wherein the label is selected from a group which consists of 5-iodo-3-pyridinecarboxylate, in part. Claim 5 embodies the composition of claim 1 wherein the ligand is a monoclonal antibody. Claim 8 embodies the composition of claim 1 wherein the ligand specifically binds to a tumor cell. Claim 9 embodies the composition of claim 1 wherein the

ligand selectively binds to EGF variant III receptor. Claim 10 embodies the composition of claim 1 wherein the ligand is a monoclonal antibody that selectively binds to EGF variant III receptor. Claim 14 embodies the composition of claim 1 wherein the oligopeptide comprises D-Lys. Claims 15 and 16 embody the composition of claim 14 wherein the oligopeptide comprises D-Arg, and at least three D-Arg, respectively. Claims 17 and 18 embody the compositions of claims 1 and 8, respectively, wherein the label comprises a radionuclide. Claims 19 and 20 embody the composition of claim 17 wherein the radionuclide is an alpha, beta or gamma emitter, and wherein the radionuclide is selected from a group consisting in part of 125-I, respectively. Claim 44 embodies the composition of claim 1 wherein the oligopeptide comprises at least two positively charged amino acids.

The abstract of Reist et al (1996) teach that anti-EGF variant III receptor antibody (L8A4) labeled with SIPC yielded an increased level of tumor to tissue ratio versus antibodies labeled with the tyramine cellobiose method. SIPC is N-succinimidyl-5-iodo-3-pyridine carboxyl ate. Zalutsky et al teach how to make N-succinimidyl-5-iodo-3-pyridine carboxyl ate and how to use said compound in the labeling of an anti-CEA antibody (columns 13-14, examples 4-6). Neither Reist et al (1996) nor Zalutsky et al teach the oligopeptide of the instant invention.

Barnett et al teach compositions comprising chemical conjugates between a carrier peptide and an agent wherein the carrier peptide facilitates the delivery of said agent into the nucleus (page 1, lines 7-9). Barnett et al teach that said carrier peptide is comprised mainly of positively charged amino acids, at least 50% of which are in the D-form (page 2, lines 9-14). Barnett et al teach that both Arg and Lys are included in the scope of positively charged amino acids (page 3, lines 28-30). Barnett et al teach the specific embodiment of [D-Arg]9 as a specific embodiment (page 9, example 1), thus fulfilling the specific embodiments of claims drawn to oligopeptide which do not comprise two or more contiguous L-amino acids and claim 44 drawn to at least two positively charged amino acids. One of skill in the art would understand that D-Lys could be substituted for any of the D-Arg in [D-Arg}9 and remain within the teachings of Barnett regarding positively charged D-amino acids, thus fulfilling the specific embodiment of claims 14-16. Barnett et al teach that the carrier peptide can be coupled to an agent which is also a peptide (page 6, lines 1-3). Barnett et al do not specifically teach the coupling of the

carrier peptide to an antibody or ligand which binds to EGF variant III receptor, or the attachment of a radionuclide or the radiolabels of the instant invention.

Woo et al teach "Although not wishing to be bound by theory, it is necessary that in order for the present .sup.125 I labeled monoclonal antibody to be effective, the monoclonal antibody must first be internalized significantly into the cell as a result of binding to its specific membrane antigen. It is believed that for maximum cell killing efficiency of a 17-1A positive tumor, the .sup.125 I radio labeled monoclonal antibody or its radioactive breakdown products, must bind directly to the nucleus. The method of the present invention provides an effective method for localizing radiation to tumor cells. The method results in the radio labeled tumor specific antibody specifically targeting the tumor cell, and the evidence provided in the Examples below indicates that the antibody is internalized into the tumor cell, and the radionuclide is thereby placed in close proximity to the tumor cell nucleus. The radiation emitted by the Auger-electron emitter particularly lethal at this close range to the tumor cell, but not to surrounding tissue, due to its subcellular range. The radiation damage to the cells is ultimately due to chromosomal damage, which results in irreparable damage to, and provides efficient killing of the tumor cells". Thus Woo et al teach the delivery of 125-I via a monoclonal antibody which is internalized and that localization of 125-I to the cell nucleus is necessary for the optimum killing of tumor cells. Woo et al do not teach the oligopeptides of the instant invention, or the ligand which binds to the EGF variant III receptor.

The abstract of Reist et al (1995) teaches that anti-EGF variant III receptor antibodies are internalized at 37 degrees and are subsequently processed intracellularly by lysosomal degradation.

The abstract of Wikstrand et al teaches that the EGF variant III receptor is internalized, but is not found within the nucleus (lines 3-8 and 24-25 of the abstract). The abstract further teaches that said variant receptor is not expressed in normal tissues but is found in gliomas, non-small cell lung and breast carcinomas and therefore provides a specific target for the selective delivery of toxins to these cancers.

It would have been prima facie obvious to incorporate the carrier peptide of Barnett into the SIPC labeled L8A4 antibody as taught by Reist et al (1996). One of skill in the art would be motivated to do so by the teachings of Woo et al on the desirability of localizing 125-I to the cell

nucleus in order to maximize damage and subsequent cell killing to the targeted cell versus the surrounding cells, and the teachings the abstract of Wikstrand et al which indicate that the internalized variant EGF receptor is not located within the nucleus and the teaching of the abstract of Reist et al (1995) which indicate that antibodies which are bound to the variant receptor are degraded within the lysosomes. One of skill in the art would be motivated to re-direct the internalized labeled antibody from the lysosomes into the nucleus in order to maximize the accumulation of 125-I within the nucleus.

The rejection of claims 1, 3-6, 8-10, 14-20 and 44-47 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199) and Zalutsky et al (U.S. 5,302,700, cited in a previous Office action) and Barnett et al (CA 209465) and Woo et al (U.S. 5,130,116) and the abstract of Reist et al (Cancer Research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140) for the reasons set forth in the rejection of claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42 and 44 above and in further view of Schlom (In: Molecular Foundations of Oncology, 1991, pp. 95-134) is maintained for reasons of record.

The specific embodiments of claims , 3-5, 8-10, 14-20 and 44 and the teachings of Reist et al (1996) and Zalutsky et al and Barnett et al and Woo et al and the abstract of Reist et al (1995), and the abstract of Wikstrand et al which render the specific embodiments of said claims obvious is set forth above.

Claims 6 embodies the method of claim 1 wherein the ligand is an interspecies recombinant antibody. Claim 45 embodies the composition of claim 1 wherein the ligand is a fragment of an antibody comprising at least a portion of an immunoglobulin light chain variable region and at least a portion of an immunoglobulin heavy chain variable region. Claim 46 embodies the composition of claim 45 wherein the fragment comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region. Claim 47 embodies the composition of claim 1 wherein the ligand comprises a single chain Fv.

Neither of said prior art references teach a recombinant antibody, an antibody fragment or a scFv.

Schlom teaches that single chain Fv antibodies are better able to penetrate a tumor mass, avoid the induction of a HAMA response and clear the blood more rapidly that whole antibodies (pages 119-123 under the heading "Single Chain Antigen Binding Proteins").

It would have been prima facie obvious at the time the invention was made to substitute a recombinant single chain Fv antibody having the variable light chain and variable heavy chain of the anti-EGF variant III receptor for the L8A4 antibody as taught by Reist et al (1996). One of skill in the art would have been motivated to do so by the teachings of Schlom who address the advantages of single chain antibodies over full antibodies.

The rejection of claims 1, 3-10, 14-20 and 44-47 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199) and Zalutsky et al (U.S. 5,302,700, cited in a previous Office action) and Barnett et al (CA 209465) and Woo et al (U.S. 5,130,116) and the abstract of Reist et al (Cancer Research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140) for the reasons set forth in the rejection of claims 1, 3-5, 8-10, 14-20, 28, 35-42 and 44 above and in further view of Schlom (In: Molecular Foundations of Oncology, 1991, pp. 95-134) is maintained for reasons of record. New claim 48 is also rejected for the following reasons of record.

The specific embodiments of claims 1, 3-5, 8-10, 14-2 and 44 and the teachings of Reist et al (1996) and Zalutsky et al and Barnett et al and Woo et al and the abstract of Reist et al (1995), and the abstract of Wikstrand et al which render the specific embodiments of said claims obvious is set forth above.

Claim 7 embodies the composition of claim 1 wherein the ligand is a humanized antibody. Neither Reist et al (1996) nor Zalutsky et al nor Barnett et al nor Woo et al nor Reist et al nor Wikstrand et al teach a humanized antibody.

Schlom teaches that following one dose of murine monoclonal antibody, approximately 50% of patients develop HAMA and that this increases to 90% in patients receiving multiple doses of murine monoclonal antibody. Schlom concludes that because of the HAMA response only the first dose of monoclonal antibody, or perhaps the first and second doses, actually reach the tumor site. Schlom states that it is unrealistic to assume that just one or two administrations

of a monoclonal antibody based cancer therapeutic to be effective. Schlom teaches that the use of chimeric and humanized antibodies can circumvent the induction of HAMA (page 98, second column bridging paragraph to page 99, first column). Schlom also teaches that Fv fragments of antibodies or single chain antibodies can be administered to reduce the HAMA response (page 99, lines 4-9), thus fulfilling he specific embodiment of a ligand which is a synthetic polypeptide..

It would have been prima facie obvious at the time the invention was made to humanize the L8A4 antibody of Reist et al (1996) or to make a single china antibody or Fv fragment from the antibody of Reist et al. One of skill in the art would have been motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response in patients receiving antibody-based therapeutics.

The rejection of claims 1, 5, 8-10, 14-16, 21 and 44 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199) in view of Barnett et al (CA 209465, full document), Woo et al (U.S. 5,130,116), the abstract of Reist et al (Cancer research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140) and Schmidt et al(US 4,614,723) is maintained for reasons of record.

The abstract of Reist et al (1995) teaches that anti-EGF variant III receptor antibodies are internalized at 37 degrees and are subsequently processed intracellularly by lysosomal degradation.

The abstract of Wikstrand et al teaches that the EGF variant III receptor is internalized, but is not found within the nucleus (lines 3-8 and 24-25 of the abstract). The abstract further teaches that said variant receptor is not expressed in normal tissues but is found in gliomas, non-small cell lung and breast carcinomas and therefore provides a specific target for the selective delivery of toxins to these cancers.

Woo et al teach "Although not wishing to be bound by theory, it is necessary that in order for the present .sup.125 I labeled monoclonal antibody to be effective, the monoclonal antibody must first be internalized significantly into the cell as a result of binding to its specific membrane antigen. It is believed that for maximum cell killing efficiency of a 17-1A positive tumor, the

.sup.125 I radio labeled monoclonal antibody or its radioactive breakdown products, must bind directly to the nucleus. The method of the present invention provides an effective method for localizing radiation to tumor cells. The method results in the radio labeled tumor specific antibody specifically targeting the tumor cell, and the evidence provided in the Examples below indicates that the antibody is internalized into the tumor cell, and the radionuclide is thereby placed in close proximity to the tumor cell nucleus. The radiation emitted by the Auger-electron emitter particularly lethal at this close range to the tumor cell, but not to surrounding tissue, due to its subcellular range. The radiation damage to the cells is ultimately due to chromosomal damage, which results in irreparable damage to, and provides efficient killing of the tumor cells". Thus Woo et al teach the delivery of 125-I via a monoclonal antibody which is internalized and that localization of 125-I to the cell nucleus is necessary for the optimum killing of tumor cells. Woo et al do not teach the oligopeptides of the instant invention, or the ligand which binds to the EGF variant III receptor.

Barnett et al teach compositions comprising chemical conjugates between a carrier peptide and an agent wherein the carrier peptide facilitates the delivery of said agent into the nucleus (page 1, lines 7-9). Barnett et al teach that said carrier peptide is comprised mainly of positively charged amino acids, at least 50% of which are in the D-form (page 2, lines 9-14). Barnett et al teach that both Arg and Lys are included in the scope of positively charged amino acids (page 3, lines 28-30). Barnett et al teach the specific embodiment of [D-Arg]9 as a specific embodiment (page 9, example 1), thus fulfilling the specific embodiments of claims drawn to oligopeptide which do not comprise two or more contiguous L-amino acids and claim 44 drawn to at least two positively charged amino acids. One of skill in the art would understand that D-Lys could be substituted for any of the D-Arg in [D-Arg}9 and remain within the teachings of Barnett regarding positively charged D-amino acids, thus fulfilling the specific embodiment of claims 14-16. Barnett et al teach that the carrier peptide can be coupled to an agent which is also a peptide (page 6, lines 1-3). Barnett et al do not specifically teach the coupling of the carrier peptide to an antibody or ligand which binds to a cell surface receptor, or the attachment of fluorescent labels to the carrier peptide.

Schmidt et al teach fluorescent labels for conjugation to antibodies (claims 11 and 24).

It would have been prima facie obvious to attach the carrier peptide of Barnett and to substitute a fluorescent label as taught by Schmidt et al for the radioactive iodine label in the composition comprising the L8A4 antibody as taught by Reist et al (1996). One of skill in the art would be motivated to do so in order to examine in vitro the amount of label accumulated in the nucleus relative to the cytoplasm. The substitution of a fluorescent label would be desirable for in vitro studies in order to eliminate the hazards associated with radioactive labeling. One of skill in the art would be motivated to re-direct the label to the cell nucleus by means of the carrier peptide taught by Barnett in light of the teachings of Woo et al regarding desirability of targeting the cell nucleus for radiolabel accumulation in order to maximize damage and subsequent cell killing to the targeted cell versus the surrounding cells, and the teachings the abstract of Wikstrand et al which indicate that the internalized variant EGF receptor is not located within the nucleus and the teaching of the abstract of Reist et al (1995) which indicate that antibodies which are bound to the variant receptor are degraded within the lysosomes.

Applicant argues that even if the teachings of the primary references were combined, the results would not unambiguosuly be the claimed composition because there is no teaching or suggestion in either of Barnett or in Reist (1996) that would direct one of skill in the art to place the SIPC label on the olgiopeptide and not the antibody and that one of ordinary skill would need to have modified the combined teachings of the cited reference to placer the label on the oligopeptide. This has been considered but not found persuasive. The combination of prior art references renders obvious the delivery of a molecule comprising a radioactive label, an antibody which targets an internalizing receptor and a oligopeptide that directs the molecule to the cellular nucleus. The options for placement of the SPIC radiolabel include either the antibody or the oligopeptide. Placing the SPIC radiolabel on the antibody would require the placement of the oligonucleotide on the antibody as well. One of skill in the art would be familiar with the pitfalls of modifying the structure of the antibody which could potentially lead to a change in antibody structure and loss of specific binding. In order to avoid this loss of antibody affinity or specificity, the antibody should only be modified to carry either the oligopeptide or the radiolabel, not both moieties. If the antibody carries the radiolabel, it is not known how to chemically link the oligopeptide to the SPIC radiolabel to produce a molecule comprising an

antibody-radiolabel-oligopeptide. Thus, the only alternative which would be expected to retain the specific binding of the antibody is linking the oligopeptide to the antibody and placing the radiolabel on the other end of said oligopeptide. Thus, the resultant molecule comprising antibody-oligopeptide-radiolabel is obvious over the prior art references. Applicant continues to argue the Barnette reference provides no motivation to combine with an antibody because said reference teaches that the oligopeptide exhibits non-specific cellular targeting. This has been considered but not found persuasive. Barnette teaches the coupling of the oligopeptide to another peptide for the delivery of the other peptide into cells. One of skill in the art would readily envision that the value of the Barnette oligopeptide is said oligopeptides ability to cause nuclear localization one in a cell and that cellular specificity can be conferred by fusion of the oligopeptide to a targeting moiety, such as an antibody which binds to a extracellular receptor which is internalized.

Claims 2, 11 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth in the prior Office action are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/26/2004